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Study of Cutaneous Adverse Drugs Reaction in Tertiary Care Hospital of Northwestern Rajasthan

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ABSTRACT

Primary aim of the present study is to estimate the burden of adverse drug reactions, to study the prevalence of different ADR's occurring in our hospital, to study severity of ADRs, to study risk factors associated with occurrence of ADRs, to propose strategies to reduce occurrence of ADRs in patients visiting to dermatology department in a tertiary care hospital. The present cross sectional observational study was conducted at Dermatology department in P.B.M. hospital, Bikaner. This study was done over a period from July 2019 to December 2019 after getting approval from institutional ethics committee. As CADRs are most common adverse drug reactions, drugs embroiled in past reaction should be avoided. A through history of previous allergies and drug hypersensitivity should be confirmed. Sensitivity testing like patch test should be done before administration of any injectable drug. In case of hypersensitivity or allergy, alternate drug should be used.

INTRODUCTION

WHO defines Adverse drug reaction (ADR) as "Any reaction which is noxious and unintended and which occurs at doses normally used in man for the prevention, diagnosis& treatment of disease".[2]

A cutaneous adverse drug reaction (CADRs) caused by a drug is any undesirable change in the structure or function of the skin, it's appendages or mucous membrane and it encompasses all adverse events related to drug eruption, regardless of etiology.[3] Although many of the skin reactions are not serious, some are life threatening such as Angioedema, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis.[4]

ADR scales were assessed initially. Different scales included were, Naranjo's causality scale, WHO scale, Schumock and Thornton preventability scale, Hartwig and Siegel severity assessment scale to assess different parameters like causality, severity and preventability.

The issue of drug-related harm is currently one of the most important public health problems all over the world, although public and scientific attention has focused on adverse drug reactions (ADRs) since the thalidomide tragedy in the early 1960s.[5]

Studies have found the overall incidence of adverse drug reactions in skin in developed countries as 1-3 % and in the developing countries it is higher between 2-5%. 5- 10% of hospital admissions are due to drug related problems, in which 50% are avoidable.[6]

In India epidemiological studies estimated that ADRs are fourth to sixth leading cause of death.[7]ADRs are one of the leading causes of morbidity and mortality, adding to overall healthcare cost. It is estimated that approximately 2.9– 5.6% of all hospital admissions are caused by ADRs and as many as 35% of hospitalized patients experience an ADR during their hospital stay.[8]

Almost any medicine can induce skin reactions, and certain drug classes, such as non-steroidal anti-inflammatory drugs(NSAIDs), antibiotics and antiepileptic drugs, have drug eruption rates approaching 1– 5%.[9] Most of the Cutaneous drug reactions are not serious but some are severe and potentially life-threatening. Serious reactions include Angioedema, Erythroderma, Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN). Drug eruptions can also occur as a result of multi-organ involvement, as in Drug-induced Systemic lupus erythematosus. Drug reactions can be classified into immunologic and

nonimmunologic etiologies. Skin reactions as a result of non-immunological causes are more common and include cumulative toxicity, overdose, photosensitivity, drug interactions, and metabolic alterations.[10]

Adverse drug reactions (ADRs) are a major cause of morbidity, hospital admission, and even death. Hence it is essential to recognize ADRs and to establish a causal relationship between the drug and the adverse event. It is desirable that ADRs should be objectively assessed and presented. Majority of Cutaneous adverse drugs reactions (CADRs) are diagnosed clinically. These reactions may differ with different classes of drugs. Generating data is essential to understand the pattern of CADRs of different classes and generating information regarding offending drugs. Adverse reactions are recognized hazards of drug therapy. Early detection, evaluation and monitoring of adverse drug reactions are essential to reduce harm to patients and thus improve public health. With the increase in the production of various pharmaceutical products, newer drugs are being introduced every year. [11]Hence it has become essential to monitor the effects and adverse drug reactions pertaining to these drugs.

We undertook this study to detect and analyse ADRs in the outpatient department of Dermatology. Developing awareness in patients and healthcare professionals will help in reducing the adverse drug reactions, the suffering due to the adverse drug reaction and socio-economic impact.

MATERIALS AND METHODS

The present cross sectional observational study was conducted at Dermatology department in P.B.M. hospital, Bikaner. This study was done over a period from July 2019 to December 2019 after getting approval from institutional ethics committee. Written and informed consent from patients were taken. In this study 100 patients visited to outpatient department of dermatology department were included, and patients with drug reaction due to deliberate or unintentional over dosage, ADR after using alternate medicines like Ayurveda, Homeopathy, Unani, Drug reaction occurring due to prescribing and dispensing error, Mentally retarded, unconscious patients, already on other Antipsychotic agents and drug abuse, critically ill, Pregnant and lactating females were excluded.

RESULTS

Table No. 1: Distribution of study population according to Thompson and Rawlins Classification

Thompson and Rawlins Classification	No.	%
Type A	88	88.0
Type B	12	12.0
Total	100	100

According to above table, 88% cases were type A and 12% cases were Type B while applying Thompson and Rawlins classification.

Table No. 2: Distribution of cases according to age group

Age Group	No of patients	%
21-30	13	13.0
31-40	41	41.0
41-50	23	23.0
51-60	21	21.0
>60	2	2.0

In our study, maximum 41% had their age between 31-40 years followed by 41-50years (23%), while minimum 2% were found in >60 years.

Table No. 3: Distribution of cases according to gender

Gender	No.	%
Female	65	65.0
Male	35	35.0
Total	100	100

In our study, 65% cases were female while 35% cases were males.

Table No. 4: Distribution of cases according to residential area

Residential area	No.	%
Rural	55	55.0
Urban	45	45.0
Total	100	100

According to residential area, majority of cases were living in rural area (55%).

Table No. 5: Distribution of cases according to adverse symptoms

Adverse Symptoms	No.	%
Redness	51	51.0
Itching	49	49.0
Rash	15	15.0
Acne	8	8.0
Eruptions	8	8.0
Hyper Pigmentation	4	4.0
Hair Loss	1	1.0
Nail Discolouration	1	1.0

According to above table, maximum 51% had redness followed by 49% cases had itching and 15% cases had rash whereas minimum 1% had hair loss and Nail discolouration followed by hyperpigmentation (4%) and acne, eruption (8%).

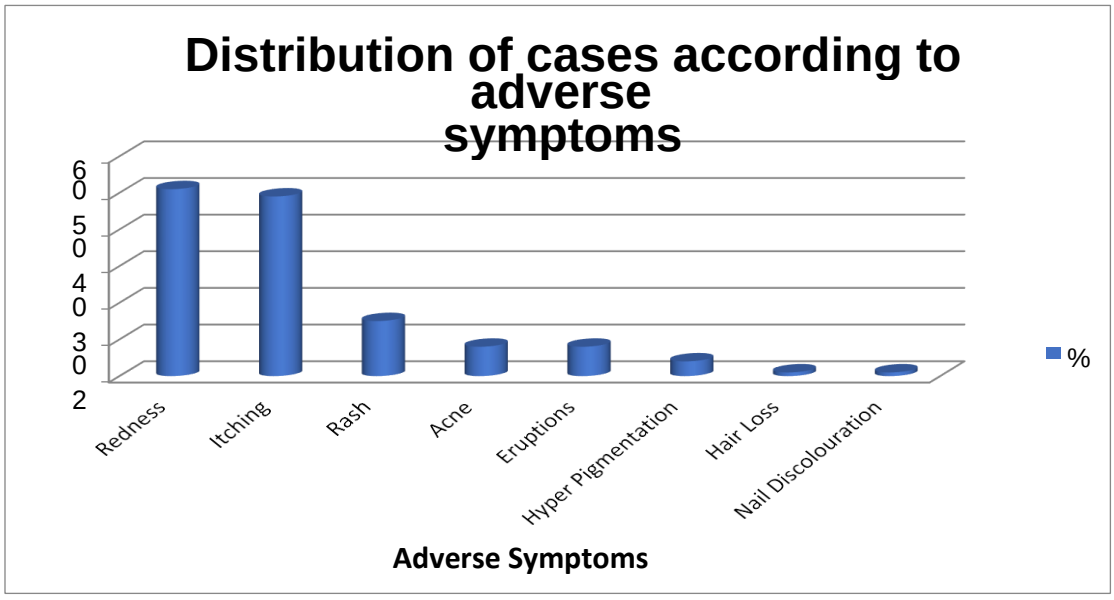

Table No. 6: Distribution of cases according to drugs

Drugs	No.	%
Oral Antibiotics	22	22.0
Topical Betnovate	19	19.0
Injectable Antibiotics	18	18.0
NSAIDs	18	18.0
Steroids	8	8.0
Topical clobetasole with gentamicin	5	5.0
Anticoagulants	4	4.0
Anti TB	2	2.0
Multivitamin	2	2.0
Anticancer	1	1.0
Iron	1	1.0
Total	100	100

According to drugs, maximum 22% taking oral antibiotics followed by topical betnovate (19%), whereas minimum 1% taking anticancer and iron drugs Followed by 2% cases each taking anti TB and multivitamin.

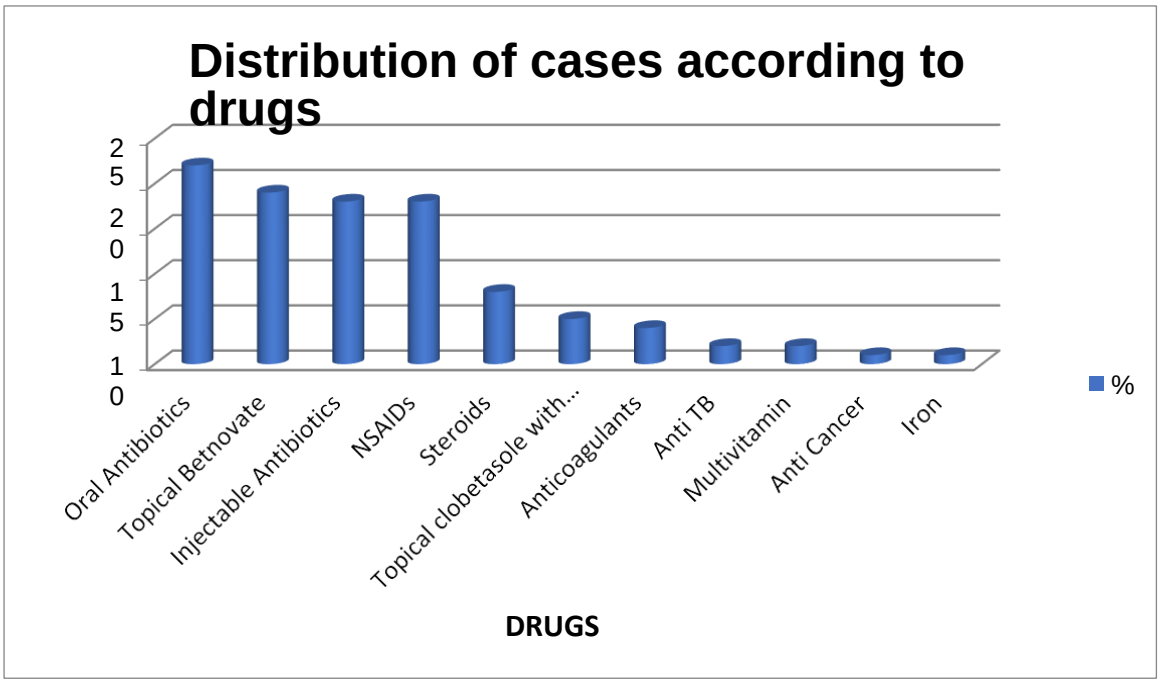

Table No. 7: Distribution of cases according to age group in relation to Thompson and Rawlins Classification

Age Group	Thompson and Rawlins Classification				Total	
	Type A		Type B			
	No.	%	No.	%	No.	%
0-20	0	-	0	-	0	-
21-30	11	12.5	2	16.7	13	13.0
31-40	36	40.9	5	41.7	41	41.0
41-50	19	21.6	4	33.3	23	23.0
51-60	20	22.7	1	8.3	21	21.0
>60	2	2.3	0	-	2	2.0
Total	88	100%	12	100%	100	100%
Mean Age	41.41		38.17			
SD	9.96		7.03			
T	1.089					
P	0.279					

Maximum 88% were type A whereas minimum 12% were Type B. Mean age in type A was 41.41□9.96 years while in type B it was 38.17□7.03. On applying student 't' test, the difference was found statistically insignificant (p>0.05).

Table No. 8: Distribution of cases according to gender in relation to Thompson and Rawlins Classification

Gender	Thompson and Rawlins Classification				Total	
	Type A		Type B			
	No.	%	No.	%	No.	%
Female	56	63.6	9	75.0	65	65.0
Male	32	36.4	3	25.0	35	35.0
Total	88	100%	12	100%	100	100%
□2	0.599					
P	0.439NS					

Majority 88% were Type A cases. 63.6% were female and 36.4% were male whereas 3/4th proportion were female in type B. On applying chi-square test, the difference was found statistically insignificant (p>0.05).

Table No. 9: Distribution of cases according to residential area in relation to Thompson and Rawlins Classification

Residential area	Thompson and Rawlins Classification				Total	
	Type A		Type B			
	No.	%	No.	%	No.	%
Rural	46	52.3	9	75.0	55	55.0
Urban	42	47.7	3	25.0	45	45.0
Total	88	100	12	100	100	100
□2	2.204					
P	0.138NS					

In type, A group study population was equally distributed whereas in type B group 3/4th proportion were residing in rural area. On applying chi-square test, the difference was found statistically insignificant (p>0.05).

Table No. 10: Distribution of cases according to adverse symptom in relation to Thompson and Rawlins Classification

Adverse Symptoms		Thompson and Rawlins Classification				Total		□2	p
		Type A		Type B					
		No.	%	No.	%	No.	%		
Redness	Absent	46	52.3	3	25.0	49	49.0		
	Present	42	47.7	9	75.0	51	51.0	3.143	0.076
Itching	Absent	48	54.5	3	25.0	51	51.0		
	Present	40	45.5	9	75.0	49	49.0	3.689	0.055
Rash	Absent	74	84.1	11	91.7	85	85.0		
	Present	14	15.9	1	8.3	15	15.0	0.475	0.491
Acne	Absent	80	90.9	12	100.0	92	92.0		
	Present	8	9.1	0	-	8	8.0	1.186	0.276
Eruptions	Absent	81	92.0	11	91.7	92	92.0		
	Present	7	8.0	1	8.3	8	8.0	0.002	0.964
Hyper Pigmentation	Absent	85	96.6	11	91.7	96	96.0		
	Present	3	3.4	1	8.3	4	4.0	0.667	0.414
Hair Loss	Absent	87	98.9	12	100.0	99	99.0		
	Present	1	1.1	0	-			0.138	0.711
Nail Discolouration	Absent	87	98.9	12	100.0	99	99.0		
	Present	1	1.1	0	-	1	1.0	0.138	0.711

Above table shows distribution of cases according to adverse symptom in relation to Thompson and Rawlins Classification. Redness was the most common adverse symptom in both type A (47.7%) and B (75.0%).75% had itching in type B. Rash was present in 15.9% and 8.3% in type A and type B respectively. Acne was present in 9.1% of type A. Eruption was present in equal cases. Hyperpigmentation was present in only 3.4% and 8.3% of type A and B cases respectively, hair loss and nail discolouration was present in 1.1% of cases in type A while Type B had no case. On applying chi-square test, all the parameters had a insignificant correlation ($p>0.05$ in all).

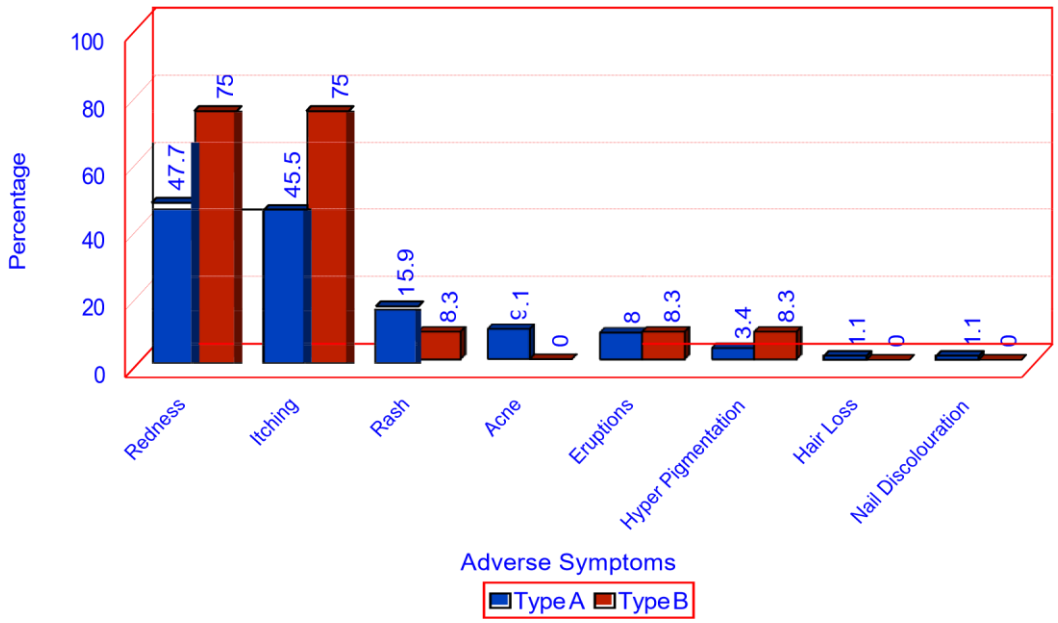

Table No. 11: Distribution of cases according to drugs in relation to Thompson and Rawlins Classification

Drugs	Thompson and Rawlins Classification				Total	
	Type A		Type B			
	No.	%	No.	%	No.	%
Anticancer	1	1.1	0	-	1	1.0
Anti TB	2	2.3	0	-	2	2.0
Anticoagulants	4	4.5	0	-	4	4.0
Injectable Antibiotics	16	18.2	2	16.7	18	18.0
Iron	1	1.1	0	-	1	1.0
Multivitamin	2	2.3	0	-	2	2.0
NSAIDs	17	19.3	1	8.3	18	18.0
Oral Antibiotics	17	19.3	5	41.7	22	22.0
Steroids	6	6.8	2	16.7	8	8.0
Topical Betnovate	17	19.3	2	16.7	19	19.0
Topical clobetasole with gentamicin	5	5.7	0	-	5	5.0
Total	88	100	12	100	100	100
□2	2.204					
P	0.138NS					

Maximum 22% patient taken oral antibiotics (maximum 42% in type B) followed by 19% topical betnovate application (maximum 16.7% in type A). Minimum 1% had taken anticancer and iron (maximum 1.1% in group A) followed by 2% anti TB and multivitamin (maximum 2.3% in group A).On applying chi-square test, the difference was found statistically insignificant (p>0.05).

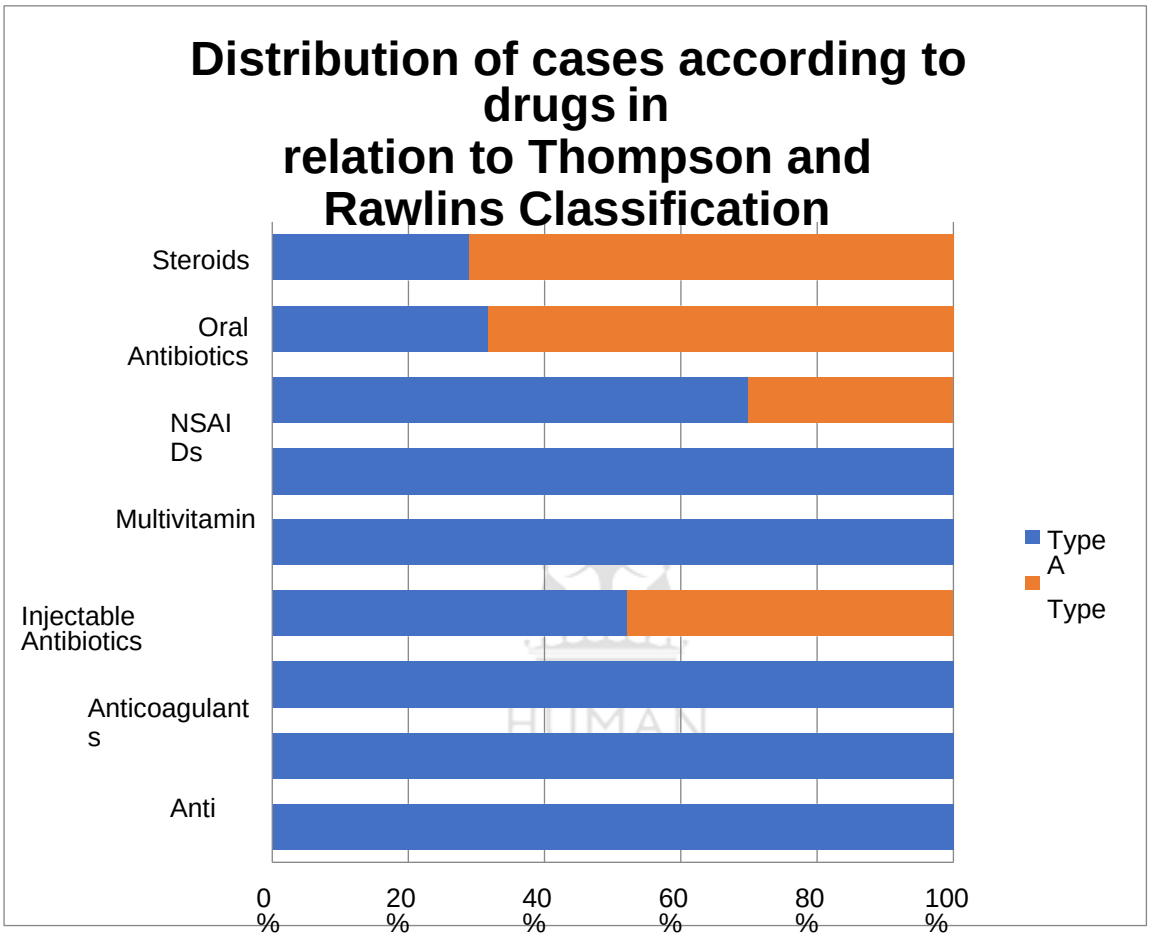

Table No. 12: Distribution of cases according to severity in relation to Thompson and Rawlins Classification

Severity	Thompson and Rawlins Classification				Total	
	Type A		Type B			
	No.	%	No.	%	No.	%
Mild	16	18.2	2	16.7	18	18.0
Moderate	62	70.5	7	58.3	69	69.0
Severe	10	11.4	3	25.0	13	13.0
Total	88	100	12	100	100	100
□2	1.749					
P	0.417NS					

According to severity, maximum 69% had moderate severity (maximum 70.5% in type A) whereas minimum 13% had severe severity (maximum 25% in type B) followed by mild severity 18% (maximum 18.2% in type A).On applying chi-square test, the difference was found statistically insignificant (p>0.05).

DISCUSSION

Drugs are used for treatment and prophylaxis of various disease conditions and are considered as safer drugs when used rationally. Drugs show some Adverse Drug Reactions in various patient conditions. Adverse Drug Reaction monitoring is an essential aspect of therapeutics. However most of the time it is overlooked and not considered important. Even when observed, many would not document and report voluntarily. Establishing pharmacovigilance units in the hospitals has facilitated this activity to a great extent. In our study, maximum number of cases had their age between 31- 40 years (41%) followed by 41-50Yrs had 23% cases, while least common age group in our study was >60 years where only 2% cases were found. Pudukadan D et al (2004), Sushma M et al (2005), SDI et al (2012), Rohini Sharma et al (2015), *Tejashwani et al (2018)*, Jagruti G. Dhanani et al (2017) found Most of cases were in the same age group. Whereas Patel Raksha M et al (2008) Maximum patients belonged to the age group 41-50. The maximum patients were in the age group of 31-40 years in our study, which is in accordance with another study that also reported similar observations. Majority 65% cases were female while 35% cases were male in our study whereas similar results were found by Pudukadan D et al (2004), SDI et al (2012) in their

studies. Whereas male preponderance was found in Sushma M et al (2005), Rohini Sharma et al (2015), Jagruti G. Dhanani et al (2017) studies. There is no big difference in the numbers of male and female. The reason of higher incidence in present study could be that females are more conscious about any dermatological reaction and treatment of ADR before it gets severe. Majority of cases in study were living in rural area (55%). According to cutaneous symptom-wise analysis, maximum number cases (51%) had redness, 49% cases had itching problem, 15% cases had rash while 8% cases each had acne and eruptions and 4% cases had hyper pigmentation while least common adverse symptoms were hair loss and Nail discolouration where only 1% cases were found. similarly, studies conducted by Shah S.P. et al, V.M. Motaghare, Sharma VK et al (2001), Pudukadan D et al (2004), Sushma M et al (2005), and *Tejashwani et al (2018) found* that most common suspected ADR was maculopapular rash followed by urticaria and/or FDE which are were also observed in the present study. Whereas Sowmyanarayan S et al was observed that the most common cutaneous ADR observed was acne vulgaris (22.86%) and generalized skin rash (22.86%) followed by fixed drug eruption (11.43%). The other cutaneous ADRs seen included Tinea cruris (8.57%), melasma (5.71%), chronic urticarial (2.9%), tinea incognita (2.9%), contact dermatitis (2.9%), toxic epidermal necrolysis (2.9%), pruritic (2.9%), atopic dermatitis (2.9%), vasculitis (2.9%), cushingoid features (2.9%) and topical atrophy (2.9%). Also, Babu L. N et al (2017) found among the skin reactions urticaria/ angioedema was the most common 109(37.2%) followed by generalised pruritus 57(19.5%) and fixed drug eruption 37(12.6%). According to drugs, 22% cases taking oral antibiotics, while 19% cases taking topical betnovate, 18% cases each were taking injectable antibiotics and NSAIDS while 8% cases taking steroids, Tropical clobetasole with gentamicin were taking 5% of cases while 4% cases taking anticoagulants, 2% cases each taking anti TB and multivitamin type Drugs while 1% each cases taking anticancer and iron drugs. In our study Mean age for Thompson and Rawlins Classification in type A was 41.41□9.96 years while in type B it was 38.17□7.03. Lesser mean age were observed by SDI et al (2012) that the patients with cutaneous drug reactions had 30.5 years. Also, Rohini Sharma et al (2015) found the mean age of the patients with CADRs was 33.26 years. Regarding ADR, Redness was the most common adverse symptom in both type A (47.7%) and B (75.0%) followed by 75% had itching in type B. Rash was present in 15.9% and 8.3% in type A and type B respectively, On contrary Ghosh S et al (2006) Majority of the adverse drug reactions (96%) were of type B on applying Thompson and Rawlins Classification.

In our study, the drugs used were maximum 22% patient taken oral antibiotics (maximum 42% in type B) followed by 19% topical betnovate application (maximum 16.7% in type A). This is quite consistent with present study that most offended drug class was antimicrobials followed by topical betnovate (steroid). Similar finding for most commaon cause of ADRs was antibiotics in other studies also but for 2nd most common cause they had different results as unknown medicines (Shah S.P. et al), NSAIDS by **Nandha et al**, V.M. Motaghare, Patel Raksha M et al (2008), Tejas K Patel et al (2014), Babu L. N et al (2017) anticonvulsants by Sharma VK et al (2001), antiepileptics by Sushma M et al (2005). On contrary Pudukadan D et al (2004) found the most common causes were co-trimoxazole (22.2%) and dapsone (17.7%). Also, Patel Raksha M et al (2008) found cotrimoxazole was the commonest drug. Also, SDI et al (2012) found most common drugs which caused the reactions were Nonsteroidal anti-inflammatory Drugs (NSAIDs) (39.1%), Quinolones (22.1%). Also, Jagruti G. Dhanani et al (2017) found Paracetamol was the most common offending drug followed by cotrimoxazole. Also, *Tejashwani et al (2018) found* NSAIDS were the most common offending drugs (16.66%), According to severity, maximum 69% had moderate severity (maximum 70.5% in type A) whereas minimum 13% had severe severity (maximum 25% in type B) followed by mild severity 18% (maximum 18.2% in type A) on applying Thompson and Rawlins Classification. On contrary, a study done by V.M. Motaghare et al had different results as, Severity assessment by modified Hartwig and Siegel's scale in the study showed that out of 18 ADRs, 8(44.44%) were mild, 8 (44.44%) were moderate and 2 (11.11%) were severe in nature. Acharya T et al had reported that the severity of adverse cutaneous drug reactions assessment to be 83% moderate and 15% mild in nature using a Hartwig and Siegel's scale.

CONCLUSION

As CADRs are most common adverse drug reactions, drugs embroiled in past reaction should be avoided. A through history of previous allergies and drug hypersensitivity should be confirmed. Sensitivity testing like patch test should be done before administration of any injectable drug. In case of hypersensitivity or allergy, alternate drug should be used.

Thus effective ADR monitoring plays a role in safety of medicines. So awareness regarding early diagnosis and prompt treatment should be spread in community and health care professionals. Reporting of CADRs should be regularly practiced by all health care providers.

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